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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte H. WILLIAM. BOSCH, KEVIN D. OSTRANDER, and
EUGENE R. COOPER

Appeal 2008-1806
Application 09/190,138
Technology Center 1600

Decided: June 23, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal[1] under 35 U.S.C. § 134 from the Examiner's final rejection of claims 11-36, 40-45, 47-49, and 51-121. We

[1] This Appeal was heard on June 10, 2007.

have jurisdiction under 35 U.S.C. § 6(b). Claims 11, 23, 35, 40, and 42-44 are the independent claims on appeal, and read as follows:

11. A dry powder aerosol composition for pulmonary or nasal delivery comprising spherically shaped aggregates formed from spray-drying aqueous dispersions of nanoparticulate drug particles, wherein:

(a) the aqueous dispersions of nanoparticulate drug particles:

(i) comprise a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml,

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000nm, and

(iii) have a surface modifier adsorbed on the surface thereof; and

(b) the aggregates of such spray-dried drug particle dispersions are less than or equal to about 100 microns in diameter; and

(c) such aggregates return to nanoparticulate drug particle dispersions upon reconstitution in an aqueous liquid medium.

23. A dry powder aerosol composition for pulmonary or nasal delivery comprising spherically shaped aggregates formed from freeze-drying aqueous dispersions of nanoparticulate drug particles, wherein:

(a) the aggregates of such freeze-dried drug particle dispersions are less than or equal to about 100 microns in diameter;

(b) the aqueous dispersions of nanoparticulate drug particles:

(i) comprise a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml,

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm,

and

(iii) have a surface modifier adsorbed on the surface thereof; and

(c) such aggregates return to nanoparticulate drug particle dispersions upon reconstitution in an aqueous liquid medium.

35. A dry powder nanoparticulate aerosol composition for use in a propellant-based pMDI comprising

(a) spherically shaped aggregates of nanoparticulate poorly soluble crystalline drug particles, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml, wherein the aggregates are less than or equal to about 100 microns in diameter, wherein such aggregates return to nanoparticulate drug particles upon reconstitution in an aqueous liquid medium, and wherein the drug particles:

(i) have a surface modifier adsorbed on the surface thereof, and

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(b) a non-aqueous propellant.

40. A method of making a dry powder nanoparticulate drug composition comprising:

(a) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles and a surface modifier adsorbed on the surface thereof, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and

(ii) the drug particles have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm; and

(b) spray-drying the nanoparticulate dispersion to form a dry powder of spherically shaped aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns, and wherein such aggregates return to a nanoparticulate drug dispersion upon reconstitution in an aqueous liquid medium.

42. A method of making a dry powder nanoparticulate drug aerosol formulation comprising:

(a) milling under non-pressurized conditions in a non-aqueous medium having a high boiling point a dispersion comprising the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a nanoparticulate drug composition having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(b) evaporating the non-aqueous medium to obtain a dry powder of spherically shaped aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns, and wherein such aggregates return to nanoparticulate drug particle dispersions upon reconstitution in an aqueous liquid medium.

43. A method of making an aerosol composition comprising:

(a) milling under pressurized conditions in a non-aqueous medium a dispersion comprising the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous dispersion medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a drug having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm;

(b) evaporating the non-aqueous medium to obtain a dry powder of spherically shaped aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns, and wherein such aggregates return to nanoparticulate drug particle dispersions upon reconstitution in an aqueous liquid medium; and

(c) formulating the dry powder spherically shaped aggregates into an aerosol composition.

44. A method of making a dry powder nanoparticulate drug composition comprising:

(a) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and wherein the drug particles have an effective average

particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(ii) a surface modifier adsorbed on the surface thereof; and

(b) freeze-drying the nanoparticulate dispersion to form a dry powder of spherically shaped aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns, and wherein such aggregates return to nanoparticulate drug particle dispersions upon reconstitution in an aqueous liquid medium.

The Examiner relies on the following references:

Edwards	US 5,985,309	Nov. 16, 1999
Dalby	US 5,202,110	Apr. 13, 1993
Liversidge	US 5,145,684	Sept. 8, 1992

Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, Ninth edition, McGraw-Hill, 1996, page 666.

We reverse.

DISCUSSION

Claims 11-34, 40, 41, 44, 45, 47, 48, 51-62, 69-96, and 111-119 stand rejected under 35 U.S.C. § 103(a) as being obvious over Edwards.

Edwards is cited for teaching aerosol particle compositions in which the particles "are less than 100 microns in diameter and have a surface modifier adsorbed thereon." (Ans. 4.) Edwards is also cited for teaching spray-drying and freeze-drying the compositions (*id.*). According to the Examiner:

> The compositions of the instant claims and those of [Edwards] do not appear to be different. Both are aerosol compositions comprising spray- or freeze-dried drug particles less than about 100 μm, and deliver an agent to the deep lung (C 9, L 59-63). Furthermore, [Edwards] teaches that varying the spray drying parameters, the aerodynamic properties of the inhaled particles

> can be effectively controlled through, for example, adjusting the inlet temperature or the feed rate and pressure of the compressed air to alter particle size (C 27, L 12-31) resulting in particle sizes that provide optimal deposition within targeted sites within the respiratory tract.

(Ans. 4.)

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we considered the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

Appellants argue that none of the references, either alone or in combination, teach the aqueous dispersions of nanoparticulate drug particles, wherein the particles have an effective average particle size of less than about 1000 nm (1 micron), wherein the particles, when freeze dried, form spherically shaped aggregates having a diameter of less than or equal to about 100 microns (App. Br.[2] 8-15).

The Examiner responds "that delivery of the drug is a matter of choice and design, and that whether in the form of aggregates or single particles, the

[2] All references to the Appeal Brief are to the Amended Brief on Appeal, date stamped October 6, 2006.

key issue is delivering the drug in a form that can reach the alveoli of the lung." (Ans. 11.)

We conclude that Appellants have the better position, and the rejection is reversed. Edwards teaches particles having a mean diameter between 5 microns and 30 microns (Edwards, col. 5, ll. 10-13). Edwards teaches further that the particles "have a larger diameter," so that they are not phagocytosed (col. 5, ll. 18-22). The Examiner has not pointed to any suggestion, either in Edwards or the knowledge of the ordinary artisan, to make the particles of Edwards smaller. Nor does Edwards teach or suggest aggregation of the nanoparticles to form a spherical aggregate having a diameter of less than or equal to about 100 microns.

Claims 11-34, 40-45, 47, 48, 51-62, 65-96, and 97-119 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Edwards and Liversidge.

Edwards is relied upon as above. Liversidge is relied upon for teaching "particle compositions that are much less than 100 microns in diameter and have a surface modifier adsorbed thereon." (Ans. 6.) According to the Examiner, after milling, "the particles are separated from the milling dispersion to yield particles that appear to be the same as those of the instant invention, absent a demonstration of criticality thereto." (*Id.*)

The Examiner concludes:

> Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of [Edwards] and [Liversidge] to provide aerosol corticosteroid particle formulations that meet the limitations of the instant claims based upon the treatment of asthma and allergies and that the rate of dissolution of a

> particulate drug can increase with increasing surface area, i.e. decreasing particle size, along with providing optimal deposition with targeted sites within the respiratory tract.

(*Id.*)

Appellants argue that Liversidge is drawn to the use of nanoparticulate compositions for oral, parental, and intravenouos administrations (App. Br. 15). Moreover, Appellants assert, "[n]either reference . . . suggests the claimed aggregate of nanoparticulate drug dispersions" (Reply Br. 25.)

We agree, and the rejection is reversed. First, as noted by Appellants, Liversidge teaches the use of nanoparticulate compositions useful for oral, parental, and intravenous administrations (Liversidge, col. 8, ll. 10-14). Second, we cannot find, nor does the Examiner point to where Liversidge teaches or suggests aggregation of the nanoparticles to form a spherical aggregate having a diameter of less than or equal to about 100 microns. Thus, Liversidge, even if combined with Edwards, does not remedy the deficiencies of Liversidge. Finally, as to the Examiners comment that "the particles are separated from the milling dispersion to yield particles that appear to be the same as those of the instant invention, absent a demonstration of criticality thereto," an obviousness rejection need address all the limitations of a claim, and not just those that the Examiner finds to be "critical" to the invention.

Claims 35, 36, 49, 63, and 64 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Edwards and Dalby.

Edwards is relied upon as above. Dalby is merely relied upon for its teaching of a "non-CFC" propellant (Ans. 8). Thus, as Dalby does not remedy the deficiencies of Edwards, the rejection is reversed.

Claims 120 and 121 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Edwards and Goodman & Gilman's.

Edwards is relied upon as above. Goodman & Gilman's is merely relied upon for its teaching that beclomethasone dipropionate is a known steroid administered for the treatment of asthma in aerosol formulations (Ans. 10). Thus, as Goodman & Gilman's does not remedy the deficiencies of Edwards, the rejection is reversed.

CONCLUSION

In summary, we find that the Examiner has not set forth a prima facie case of obviousness as to any of the claims on Appeal, and the rejections are therefore reversed.

REVERSED

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